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Review of adverse cutaneous reactions of pharmacologic interventions for COVID-19: A guide for the dermatologist

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The new coronavirus, severe acute respiratory syndrome coronavirus 2, is associated with a wide variety of cutaneous manifestations. Although new skin manifestations caused by COVID-19 are continuously being described, other cutaneous entities should also be considered in the differential diagnosis, including adverse cutaneous reactions to drugs used in the treatment of COVID-19 infections. The aim of this review is to provide dermatologists with an overview of the cutaneous adverse effects associated with the most frequently prescribed drugs in patients with COVID-19. The skin reactions of antimalarials (chloroquine and hydroxychloroquine), antivirals (lopinavir/ritonavir, ribavirin with or without interferon, oseltamivir, remdesivir, favipiravir, and darunavir), and treatments for complications (imatinib, tocilizumab, anakinra, immunoglobulins, corticosteroids, colchicine and low molecular weight heparins) are analyzed. Information regarding possible skin reactions, their frequency, management, and key points for differential diagnosis are presented. (J Am Acad Dermatol 2020;83:1738-48.)

Key words: COVID-19 drug treatment; drug eruptions; drug-related side effects and adverse reactions; review.

The new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is spreading rapidly worldwide. To date, there are no proven effective therapies for this virus. Knowledge about SARS-CoV-2 virology is rapidly increasing, and a large number of potential drug targets are being investigated.[1] Currently, infection management is mainly supportive, and common drugs prescribed for infection control include antimalarials (chloroquine and hydroxychloroquine), lopinavir/ritonavir, ribavirin, interferon, oseltamivir, remdesivir, favipiravir, and darunavir. Drugs prescribed for complications associated with viral infections include anticytokines (mainly interleukin [IL] 6 blockers and anakinra), imatinib, corticosteroids, colchicine, heparins, immunoglobulins, and hyperimmune plasma.[2]

Cutaneous manifestations have recently been described in patients with the new coronavirus infection, similar to cutaneous involvement occurring in common viral infections.[3-5] A recently published nationwide consensus study in Spain has widely described these manifestations in a prospective study with 375 cases. In this case collection survey, authors described 5 clinical patterns: acral areas with erythema-edema associated with some vesicles or pustules (pseudo-chilblain lesions), maculopapular eruptions, urticaria, other vesicular lesions (monomorphic disseminated vesicular lesions and acral vesicular-pustulous lesions), and livedo or necrosis.[6]

The diagnosis of cutaneous manifestations in patients with SARS-CoV-2 infection is challenging for dermatologists.[7,8] It remains unclear whether these lesions are related to the virus. Skin diseases not related to coronavirus, other seasonal viral infections, and drug reactions should be considered in the differential diagnosis, especially in those patients with nonspecific manifestations such as urticaria or maculopapular eruptions. However, some features may help distinguish COVID-19 cutaneous lesions from drug-related ones. Urticarial

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lesions and maculopapular eruptions in SARS-CoV-2 infections usually appear at the same time as the systemic symptoms, whereas drug adverse reactions are likely to arise hours to days after the start of the treatment.[6,9] The aim of this review is to provide dermatologists with an overview of the cutaneous adverse effects associated with the most frequently prescribed drugs in patients with COVID-19, serving as a guide to assist dermatologists and other physicians in differential diagnosis.

CAPSULE SUMMARY

- Severe acute respiratory syndrome coronavirus 2 infection has been associated with multiple cutaneous manifestations, such as maculopapular eruption, pseudo-chilblain lesions, urticaria, monomorphic disseminated vesicular lesions, acral vesicular-pustulous lesions, and livedo or necrosis.
- Many treatments prescribed for COVID-19 may cause a wide variety of cutaneous adverse effects that should be considered in the differential diagnosis.

ANTIMALARIALS

Hydroxychloroquine and chloroquine are antimalarials that have been widely used in the treatment of some chronic inflammatory diseases. They are currently being investigated in more than 160 clinical trials[10] and have been approved for the treatment of COVID-19 by the US Food and Drug Administration (FDA) as an Emergency Use Authorization and by the European Medicines Agency for hospitalized patients in the context of clinical trials or as part of national emergency programs.[11,12] Although their mechanisms of action against SARS-CoV-2 are not fully understood, both drugs may change the pH at the cell membrane surface and inhibit viral fusion and glycosylation of viral proteins. Moreover, hydroxychloroquine can also inhibit nucleic acid replication and viral assembly.[13,14] Despite the lack of high-quality scientific articles, several studies have shown improved survival of patients with COVID-19 who were treated with antimalarials. Although 2 studies showed an increased mortality in patients treated with antimalarials, these articles have been retracted because the authors cannot vouch for the veracity of the data.[15,16] Both treatments are generally well tolerated, with retinopathy being the best known adverse effect. However, cutaneous adverse events might appear in up to 11.5% of patients,[17] and some of them can be mistaken for skin manifestations of SARS-CoV-2, especially those with maculopapular rash or exanthematous reactions. This itchy maculopapular eruption tends to appear 2 weeks after the start of the treatment, mainly on the trunk and limbs, and may mean that treatment has to be stopped in some patients.[18-20] Exacerbation of psoriasis is probably the most common cutaneous adverse effect that appears during treatment with antimalarials, with some cases described in patients with autoimmune diseases and also with COVID-19. Lesions of plaque psoriasis, pustular psoriasis, inverse psoriasis, and even erythroderma have been described in patients undergoing treatment with chloroquine and hydroxychloroquine.[21-24] It is important to screen for a personal history of psoriasis in patients with COVID-19 who are candidates for antimalarials to prevent severe flares.[25] Cutaneous hyperpigmentation is another well-known skin adverse effect of antimalarial agents that usually appears after long-term treatment, especially under chloroquine treatment. Melanonychia and mucosal pigmentation can also appear because of the high drug binding of both chloroquine and hydroxychloroquine and frequently arise months or years after the beginning of treatment.[26-28] Other cutaneous adverse events have been described[29-31] and are detailed in Table I[32-36] with their general approach.

LOPINAVIR/RITONAVIR

Lopinavir/ritonavir is an oral agent approved for treating HIV infections. This combination may have a role to play in the treatment of other coronavirus infections such as SARS-CoV-1 or Middle East respiratory syndrome (MERS) through 3-chymotrypsin–like protease inhibition.[37,38] Its use in the treatment of COVID-19 is currently being investigated, after observing promising results in case reports and case series.[39,40] There are more than 30 registered clinical trials involving lopinavir/ritonavir for the treatment of COVID-19,[10] although the results of 1 trial conducted on adult patients hospitalized with severe COVID-19 did not show significant benefits beyond standard care. In this study, the mean time to start treatment was 13 days.[41] Cutaneous adverse reactions are among the most common adverse effects in patients treated with lopinavir/ritonavir. According to HIV studies, skin rashes may appear in 5% of adult patients and up to 12% of children. This maculopapular pruritic rash often starts shortly after the start of treatment and is usually well tolerated, although Steven-Johnson syndrome (SJS) associated with serious multiorgan toxicity has been described.[42-44] In patients with HIV treated with this combination, inflammatory, painful leg edema appearing 3 or 4 weeks after starting the treatment has been described, which might be

Abbreviations used:

FDA:	US Food and Drug Administration
IL:	interleukin
MERS:	Middle Eastern respiratory syndrome
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
SJS:	Stevens-Johnson syndrome

associated with skin rash.[45,46] Alopecia areata has also been reported as an infrequent and delayed adverse reaction, and treatment needs to be discontinued for improvement to occur.[47,48] Other cutaneous adverse events[49-53] are detailed in Table I.

RIBAVIRIN/INTERFERON

Systemic ribavirin, a guanine analogue that inhibits RNA polymerase and has been used in chronic hepatitis C virus infection, is currently being investigated as a treatment for COVID-19 in 3 clinical trials,[10] although previous studies in patients with SARS-CoV-1 and MERS showed no significant effectiveness.[54,55] This drug is usually combined with interferon in both hepatitis C virus and in COVID-19 infections because of the activity of interferon against MERS.[56] Drug-induced skin reactions are among the most common adverse effects of both drugs, and their global incidence has been estimated at 13% to 23%.[57,58] A wide range of cutaneous manifestations have been described[59-62] (Table I).

OSELTAMIVIR

Oseltamivir is a neuraminidase inhibitor that was successfully used during the 2010 influenza H1N1 outbreak. At the beginning of the SARS-CoV-2 pandemic, oseltamivir was used in many patients, but recent clinical trials did not show significant effectiveness. It is currently being investigated in 6 clinical trials.[10] Cutaneous adverse effects are unusual, but the appearance of SJS and toxic epidermal necrolysis should be monitored, especially in children.[63,64]

REMDESIVIR

Remdesivir (GS-5734) is a nucleotide analogue prodrug that inhibits viral RNA polymerases.[65] It was developed to treat Ebola disease and other RNA viruses,[66] and it has been shown to have potent in vitro activity against SARS-CoV-2 by interfering with NSP12.[14] Its effectiveness in the treatment of COVID-19 is currently being tested in 11 ongoing randomized trials.[10] It has been approved by the FDA as an Emergency Use Authorization,[11] and as of July 3, 2020, the European Commission granted its conditional marketing authorization for the treatment of COVID-19 in adults and adolescents (from 12 years of age and weighing at least 40 kg) with pneumonia requiring supplemental oxygen.[12] Although there is little information on remdesivir adverse events, cutaneous manifestations may not be very frequent. A randomized controlled trial assessing investigational therapies for Ebola disease showed cutaneous adverse events in 1.7% (3/175) of patients treated with remdesivir.[67] More recently, a cohort of 53 patients receiving a 10-day course of remdesivir were followed up, and 7.55% (4/53) had developed a cutaneous rash.[68] Nevertheless, no information is provided about rash morphology, distribution, or timeline in relation to remdesivir that may help clinicians differentiate from cutaneous manifestations of COVID-19.[69] A combination of oral antihistamines and topical corticosteroids could be an effective treatment for this adverse event.

FAVIPIRAVIR

Favipiravir (T-705) is an antiviral triphosphate that inhibits RNA polymerase, blocking viral replication. It was approved in Japan for treating pandemic influenza virus infections and was also used off label to treat patients infected with the Ebola virus and the Lassa virus.[70] It is also currently being considered for the treatment of COVID-19 in 14 clinical trials.[10] To our knowledge, no adverse cutaneous events have been reported to date.[71-73]

DARUNAVIR

Darunavir, a protease inhibitor used against HIV infections, may also have potential efficacy in treating COVID-19[74] and is being investigated at this time in 2 clinical trials.[10] Maculopapular rash is a common adverse event associated with darunavir[75-77] and should be differentiated from rashes related to COVID-19.[69] The median interval between darunavir initiation and rash development is 14 days (range, 1-150 days), and a previous history of rashes linked to non-nucleoside reverse transcriptase inhibitors is a risk factor for darunavir-related rashes.[75] Although darunavir-related rashes are often self-limiting and usually mild to moderate in severity,[77,78] they can occasionally be severe, without improvement after treatment with oral antihistamines or steroids, in which case it is necessary to discontinue darunavir treatment.[75] Other cutaneous manifestations are detailed in Table I.[77-79]

IMATINIB

Imatinib, a tyrosine kinase inhibitor, is another drug that may be effective in treating COVID-19 and that is currently being investigated in 4 clinical

Table I. Adverse cutaneous events related to the most frequently used drugs in COVID-19

Drug	Morphology of cutaneous eruption	Frequency	Key points for differential diagnosis with skin manifestations of COVID-19	How to manage the adverse cutaneous effect
Antimalarials	Pigmentation disorders	4.9% to 29%	Personal history of psoriasis	Symptomatic (antihistamines ± topical or systemic corticosteroids) in mild to moderate cases
	Maculopapular rash	Up to 11.5%	Chronology of drug introduction and onset of symptoms	
	Exanthematous reactions			
	DRESS syndrome		Complete blood count (eosinophilia in DRESS syndrome)	Treatment discontinuation in severe cases
	AGEP			
	Psoriasis exacerbations		Complete metabolic panel to assess renal and liver function may be considered.	
	Erythema multiforme			
	Systemic eczematous contact dermatitis		Biopsy in severe cases with diagnostic doubts*	
Lopinavir/ Ritonavir	Maculopapular rash	5% adults/12% children	Chronology of drug introduction and onset of symptoms (a few days in the case of rash and SJS, 3-4 wk in the case of leg edema)	Symptomatic (antihistamines ± topical or systemic corticosteroids) in mild to moderate cases
	SJS	<1%		
	Leg edema			Treatment discontinuation in severe cases
	Alopecia areata		Biopsy in severe cases with diagnostic doubts*	
	Skin infections			
	Exfoliative erythroderma			
	Lichenoid eruptions			
	Urticaria			
	Pruritus			
	Xeroderma			
	Oral mucosa lesions			
	Redistribution of body fat, facial wasting, cysts, and ingrown toenails	Delayed		
Ribavirin +/− interferon	Eczematous drug reactions	10.3% to 23%	Chronology of drug introduction and onset of symptoms	Symptomatic (antihistamines ± topical or systemic corticosteroids) in mild to moderate cases
	Xerosis and pruritus			
	Maculopapular rash	1% to 4%	Biopsy in severe cases with diagnostic doubts*	Treatment discontinuation in severe cases
	Psoriasis			
	Lichenoid eruptions			
	Alopecia	8.1% to 19%		
Oseltamivir	SJS	<1%	Special attention in children	Treatment discontinuation
	TEN		Chronology of drug introduction and onset of symptoms	
			Biopsy in severe cases with diagnostic doubts*	
Remdesivir	Maculopapular rash	1.7% to 7.5%	Chronology of drug introduction and onset of symptoms	Symptomatic (antihistamines ± topical or systemic corticosteroids)

Continued

Table I. Cont'd

Drug	Morphology of cutaneous eruption	Frequency	Key points for differential diagnosis with skin manifestations of COVID-19	How to manage the adverse cutaneous effect
Darunavir	Maculopapular rash Thrombocytopenic purpura Vesicular rash Allergic dermatitis SJS TEN	~10% <1% <1% <1% <1% <1%	Previous history of reactions with non-nucleoside reverse transcriptase inhibitors Chronology of drug introduction and onset of symptoms (median, 14 d in the case of rash) Biopsy in severe cases with diagnostic doubts*	Rash is usually self-limiting. Symptomatic (antihistamines ± topical or systemic corticosteroids) in mild to moderate cases Treatment discontinuation in severe cases
Imatinib	Maculopapular rash Edema Pigmentary disorders Lichenoid reactions Psoriasiform eruption Pityriasis rosea–like eruption AGEP SJS Urticaria Neutrophilic dermatosis Photosensitivity Porphyria and pseudoporphyria	20% to 67% 48% to 65% 4% to 40% <1% <1% <1% <1% <1% <1% <1% <1% <1%	Complete blood count (eosinophilia) Chronology of drug introduction and onset of symptoms (median, 2.8 mo in the case of rash) Biopsy in severe cases with diagnostic doubts*	In the case of rash, symptomatic treatment with antihistamines and/or topical corticosteroids Systemic corticosteroids and modification of the imatinib regimen are not usually necessary. In other severe cases, treatment discontinuation should be considered.
Tocilizumab	Maculopapular rash Urticaria Cellulitis Necrotizing fasciitis Cutaneous sarcoidosis Pustular eruptions	>10%: rash, urticaria, cellulitis <1%: necrotizing fasciitis, cutaneous sarcoidosis, pustular eruptions	Chronology of drug introduction and onset of symptoms (rash and urticaria) Bacterial cultures and imaging tests (cellulitis and necrotizing fasciitis) Biopsy in severe cases with diagnostic doubts*	Symptomatic (antihistamines ± topical or systemic corticosteroids) in mild to moderate cases Treatment discontinuation in severe cases
Anakinra	Injection site reaction Generalized urticarial rash	13.8% to 14.6% <1% to 4%	Chronology of drug introduction and onset of the symptoms Vigilance of anakinra dosage Biopsy in severe cases with diagnostic doubts*	Dosage reduction or treatment discontinuation Desensitization
Immunoglobulins	During the infusion: Urticarial plaques Delayed: Maculopapular rash Eczema Erythema multiforme Purpuric erythema	>10% <1%	Chronology of drug introduction and onset of symptoms Biopsy in severe cases with diagnostic doubts*	During the infusion: stop the infusion and administer oral/intravenous diphenhydramine or corticosteroids. Consider premedication with these drugs in patients with previous reactions Delayed: antihistamines and/or topical/systemic corticosteroids

Corticosteroids	Skin thinning	51% to 73.1%	Chronology of drug introduction and onset of symptoms	Treatment discontinuation when possible
	Purpura and telangiectasia	7.1% to 23.3%	Biopsy in severe cases with diagnostic doubts*	Acne vulgaris treatment[32] in the case of steroid acne
	Hypertrichosis	15.8% to 39.1%		Antibiotics/antifungals/antivirals in the case of skin infections
	Hair loss	9.9% to 27.6%		
	Stretch marks	7.1% to 23.3%		
	Risk of skin infections (malassezia folliculitis, cutaneous candidiasis, bacterial cellulitis, or herpes zoster)	~7%		
	Steroid acne (monomorphic follicular papulopustules that favor the chest and back)	0.3% to 8.7%		
Colchicine	Alopecia Morbilliform rash Bullous dermatitis Erythema nodosum–like lesions TEN-like reactions	<1% (mainly cases of intoxication; other symptoms include diarrhea and gastrointestinal symptoms, rhabdomyolysis, renal and heart failure, bone marrow suppression, and multiorgan failure)	Vigilance of colchicine dosage Complete blood count and renal function Biopsy in severe cases with diagnostic doubts* (Although not common, the presence of metaphase-arrested keratinocytes on skin biopsy is useful for the diagnosis)[113]	Dosage reduction or treatment discontinuation Supportive care[33,34]
LMVH	Heparin-induced skin necrosis (erythematous plaques, hemorrhagic blisters, necrotic ulcers, and petechiae)	<1%	Complete blood count (relative decrease in platelet count) Detection of heparin-platelet factor 4 Chronology of drug introduction and onset of symptoms (5-10 d, or less if previously sensitized)[35] Biopsy in severe cases with diagnostic doubts* (platelet thrombi in the dermal vessels)	Rapid discontinuation of LMWH (if not, it can lead to fatal complications such as limb ischemia or myocardial or cerebral infarction)[118] and administration of anticoagulants such as danaparoid or argatroban Standard wound care for skin necrosis[36]

AGEP, Acute generalized exanthematous pustulosis; *DRESS,* drug reaction with eosinophilia and systemic symptoms; *LMWH,* low-molecular-weight heparins; *SJS,* Steven-Johnson syndrome; *TEN,* toxic epidermal necrolysis.
*In certain circumstances/clinical presentations, a skin biopsy may not be able to differentiate drug versus virus-induced eruption.

trials.[10] Its activity occurs in the early stages of infection, after internalization and endosomal trafficking, by inhibiting the fusion of the virions at the endosomal membrane.[80] More than 20% of patients treated with imatinib may develop a rash, presenting as erythematous and maculopapular lesions.[81] The median time to develop a severe rash requiring major interventions was 2.8 months (range, 0.2-8.4 mo). Serial eosinophil blood levels during imatinib treatment showed direct correlation with the development of erythematous and maculopapular skin rash and its severity. Major interventions, including systemic steroids and imatinib dose modification/reduction, are rarely needed (5%), and discontinuation is extremely rare.[81] Other cutaneous manifestations are detailed in Table I.[82-86]

ANTICYTOKINE OR IMMUNOMODULATORY AGENTS

Different monoclonal antibodies against cytokines potentially involved in the so-called cytokine storm, a dysfunctional stimulation of the immune system leading to organ damage, have been proposed for the management of COVID-19.[87] Tocilizumab, an IL-6 blocker, is the most investigated drug in this field,[2] and it is being used at this time in more than 30 clinical trials.[10] Its cutaneous manifestations may be divided into true cutaneous adverse effects (urticarial, purpuric, and ulcerating lesions) and those secondary to infection.[88] The most common adverse cutaneous reactions to tocilizumab are maculopapular rash, urticaria, and cellulitis.[89,90] Necrotizing fasciitis, cutaneous sarcoidosis, and pustular eruptions have also been reported.[91-93] Maculopapular rash and urticarial lesions will be the main differential diagnosis for skin manifestations of COVID-19.[69] Treatment will require the use of antihistamines and corticosteroids. Although less frequent, the increased risk of skin infections associated with IL-6 blockers should always be considered, because cellulitis and necrotizing fasciitis can be life-threatening conditions that must be adequately and promptly treated.

Anakinra, an IL-1 receptor antagonist, is currently under investigation for use in the treatment of COVID-19–associated pulmonary complications with elevated IL-6 levels. To date, up to 17 clinical trials are investigating its use in COVID-19.[10] A recent retrospective cohort study has shown significant clinical improvement with high doses in patients with COVID-19 with acute respiratory distress syndrome and hyperinflammation.[94] Mild injection site reaction is the most common cutaneous adverse effect during anakinra treatment. However, some investigators have reported the occurrence of severe cutaneous urticarial rash in several patients, which means treatment has to be discontinued. Clinical improvement of the cutaneous rash has been noted after treatment cessation.[95-97]

IMMUNOGLOBULIN THERAPY

Immunoglobulin therapy consists of the use of hyperimmune immunoglobulins or plasma from recovered patients. These antibodies can help clear the free circulating virus and infected cells.[98] Its use in the treatment of COVID-19 is currently being investigated in more than 70 clinical trials,[10] and the FDA is supporting and coordinating research in this field.[99,100] Cutaneous adverse reactions in the form of urticarial plaques during the infusion are common, whereas delayed skin reactions in the form of eczema, erythema multiforme, purpuric erythema, or maculopapular rash are infrequent.[101-103] Slowing the infusion rate of immunoglobulin could help reduce infusion reactions.[101] In the presence of compatible infusion-related skin lesions, the infusion should be temporarily discontinued, and treatment with oral/intravenous diphenhydramine or corticosteroids may be administered.[104] Moreover, patients may infrequently develop systemic sensitivity to immunoglobulin therapy, including anaphylaxis/anaphylactic reactions. In patients with skin reactions to previous infusions, premedication with diphenhydramine and/or corticosteroids should be considered. Delayed skin reactions can be safely treated with antihistamines and/or topical or systemic corticosteroids. COVID-19 infection can produce urticarial rash and purpuric erythema,[69,105,106] which should be distinguished from these reactions.

SYSTEMIC CORTICOSTEROIDS

Data on the use of systemic corticosteroids in COVID-19 infection are controversial, although they have been proposed to control the cytokine storm[87] and are also required for shock or exacerbation of chronic obstructive pulmonary disease.[2] Their use is currently being investigated in more than 15 clinical trials.[10] Recently, the preliminary results of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial showed that dexamethasone compared to standard care reduced 28-day mortality by a third in patients receiving invasive mechanical ventilation and by a fifth in patients receiving oxygen without invasive mechanical ventilation; the mortality rate did not change in patients not receiving respiratory support.[107] The most common adverse cutaneous events, most of them largely delayed, and their general approach are detailed in Table I. With regard to differential diagnosis of cutaneous manifestations of COVID-19, the vascular fragility

associated with corticosteroid use, especially in elderly patients, may be similar to the thrombotic complications of COVID-19 infection.[108,109]

COLCHICINE

Colchicine has been proposed for the treatment of COVID-19.[110] It is currently being investigated for the treatment of COVID-19 in more than 10 clinical trials.[10] Cutaneous adverse events with colchicine are very infrequent, mainly occurring because of intoxication (Table I).[111-115]

LOW-MOLECULAR-WEIGHT HEPARINS

Low-molecular-weight-heparins are recommended for all in-patients to prevent thrombotic complications,[116] and more than 15 clinical trials are investigating their use in COVID-19 at this time.[10] Heparin-induced skin necrosis is the most important adverse cutaneous event[117] (Table I). Lesions can occur at the injection site or at a distance.[118] The diagnosis is usually clinical. Other complementary tests and management are detailed in Table I.

CONCLUSIONS

This new virus is encouraging physicians and scientists to expand their knowledge and describe new findings associated with the disease, including in the field of dermatology. Moreover, the number of investigational drugs is increasing daily. By considering adverse drug reactions in the differential diagnosis, dermatologists can be useful in assisting in the care of these patients. Although the frequency of drug eruption in patients with COVID is currently unknown, drugs may be the causal agent of skin reactions in some patients. There are a wide variety of skin reactions, some of which may be confused with cutaneous manifestations of COVID-19. Diagnosis is usually clinical, and skin biopsy or other complementary tests are generally reserved for severe cases. Management is often symptomatic, but it is sometimes necessary to modify or discontinue the treatment, and some conditions can even be life-threatening.

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